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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,898	10/31/2001	Richard E. Fine	3928/1J861-US1	9001

7590 07/11/2003

DARBY & DARBY P.C.  
805 Third Avenue  
New York, NY 10022

EXAMINER
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NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 07/11/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	10/001,898	FINE ET AL.
	Examiner Christopher Nichols, Ph.D.	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) Responsive to communication(s) filed on 01 May 2003.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) 1-7 and 13-15 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 8-12 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 31 October 2001 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>3-6</u>	6) <input type="checkbox"/> Other: _____

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of Group II (claims 8-12) drawn to a method of purifying dense core vesicles (DCVs) in Paper No. 10 (1 May 2003) is acknowledged. Claims 1-7 and 13-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

### ***Status of Application, Amendments, and/or Claims***

2. The Preliminary Amendment filed 7 March 2002 (Paper No. 4) has been received and entered in full.

### ***Drawings***

3. The drawings are objected to because Figure 6A-6D contain reference bars with "200" over them but not accompanying units. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

### ***Specification***

4. The disclosure is objected to because of the following informalities: the description of Figure 6 does not include a description of 6B and 6C (pp. 5 lines 7-11); unnecessary period "pH 7.4," (pp. 13 line 29). Appropriate correction is required.

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (pp. 11 lines 19-20). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

***Claim Objections***

6. Claim 8 is objected to because of the following informalities: “cetrifugating” is misspelled. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 8-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method of purifying dense core vesicles which method comprises*

- (a) *centrifugating a resuspended pellet after homogenization of nerve and termini from dissected brain samples in order to obtain a microsome preparation;*
- (b) *separating said microsome preparation by a sucrose velocity size gradient wherein the gradient levels are between 29-42% for 2 hours at 100,000xg;*

*(c) centrifugating said microsome preparation onto a sucrose pad to yield a purified product; and*

*(d) collecting a quantity of the purified product from a sucrose equilibrium density gradient wherein the gradient levels are between 38.5-45.5% for 18 hours at 92,000xg,*

does not reasonably provide enablement for *other gradient centrifugation protocols*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

8. The above invention is drawn to a method of using a combination of velocity size gradient centrifugation followed by equilibrium density gradient centrifugation to purify dense core vesicles. The specification teaches that a method wherein sucrose velocity size gradient centrifugation for 2 hours at 100,000xg with gradient levels between 29-42% sucrose followed by a sucrose equilibrium density gradient centrifugation of 92,000xg for 18 hours will yield a substantially purified product of dense core vesicles from homogenized nerve and termini from dissected brain samples.

9. The language of said claims encompasses several varieties of gradient centrifugation materials including but not limited to Ficoll, Percoll, BSA, and sucrose as well as any speed or duration for the centrifugation steps. Since the specification fails to provide any guidance for the successful use of other gradient materials and other speed and time protocols for centrifugation purification are highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation.

10. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using other gradient centrifugation protocols to

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isolate dense core vesicles. Additionally, a person skilled in the art would recognize that predicting the efficacy of using any given gradient centrifugation protocol to purify dense core vesicles based solely on the performance of a single protocol is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the other gradient materials, durations, and centrifugation force values to purify dense core vesicles, such a disclosure would not be considered enabling since the state of gradient centrifugation is labor intensive and unpredictable. The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. The following references are cited herein to illustrate the state of the art of gradient centrifugation.

12. Schuck *et al.* (February 2002) "Size-Distribution Analysis of Proteins by Analytical Ultracentrifugation: Strategies and Application to Model Systems." Biophysical Journal **82**(2): 1096-1111 teaches the difficulties of predicting size-distributions from sedimentation velocity protocols (pp. 1108-1111). While concerned with proteins, Schuck *et al.* (2002) nevertheless discusses issues important in considering the variables for vesicle purification protocols.

13. In further support, the Examiner has supplied an excerpt from the reference Principles of Biochemistry 5<sup>th</sup> Ed. (1973) detailing the variables and parameters to take into consideration

when determining gradient centrifugation protocols (pp. 128-137; pp. 302-304). It is clear from *Principles of Biochemistry* 5<sup>th</sup> Ed. (1973) that the size, weight, shape of the target whether it be a protein or a dense core vesicle must be taken into consideration for a successful purification protocol leave an undue burden of experimentation on the skilled artisan to practice the invention to the full scope as claimed.

14. Moreover Day *et al.* (1971) "Zonal Centrifuge Profiles of Rat Brain Homogenates: Instability in Sucrose, Stability in Iso-osmotic Ficoll-Sucrose." Analytical Biochemistry 39(1): 29-45, Carlson *et al.* (4 April 1978) "Purification of Synaptic Vesicles from Elasmobranch Electric Organ and the Use of Biophysical Criteria to Demonstrate Purity." Biochemistry 17(7): 1188-1199, and Lubetzki *et al.* (1991) "Morphological, Biochemical, and Functional Characterization of Bulk Isolated Glial Progenitor Cells." Journal of Neurochemistry 56(2): 671-680 teach that gradient centrifugation methods entail a great deal of trial and error along with *de novo* determinations of the effects of biophysical properties on purity. Thus the skilled artisan is confronted with a tremendous burden of experimentation in an unpredictable art to practice the invention to its full scope.

15. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known gradient materials, time, and g-force combinations-- a triple variable calculation [see Galembeck and Costa (1987) "The Osmosedimentation Effect: Its Application to Chemical and Biochemical Separation." Brazilian J. Med. Biol. Res. 20(3-4): 297-312]. In the absence of any guidance from the specification, the

amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

16. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from a single centrifugation protocol to the a wide range of possible and encompassed protocols as exemplified in the references above.

17. **It is noted that Applicant can obviate the above rejection by incorporating the limitations of claims 9, 10, 11, and 12 into the independent claim 8.**

18. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: (a) the time and force at which the centrifugation steps are to be carried out, (b) the type of equilibrium density gradient.

19. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. The term "low speed" in claim 9 is a relative term which renders the claim indefinite. The term "low speed" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear from the instant Specification or the prior art as to what constitutes "low speed" for the claimed method. Applicant may obviate this rejection by including a "g" force value and a time of centrifugation.

21. Claim 10 recites the limitation "final quantity" in the first line. There is insufficient antecedent basis for this limitation in the claim.

22. Claim 12 recites the limitation "sucrose equilibrium density gradient" in the second line. There is insufficient antecedent basis for this limitation in the claim.

*Summary*

23. Claims 8-12 are hereby rejected.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

*Elizabeth C. Kemmerer*

CJN  
July 3, 2003

ELIZABETH KEMMERER  
PRIMARY EXAMINER